

**REMARKS**

Support for the amendment to claim 1 can be found on page 1, lines 31-34 of the specification. Claim 2 has been amended to be dependent on claim 1. The amendments to the specification are made to correct obvious typographical errors which the examiner had pointed out in the Office Action. No new matter has been introduced through any of the amendments above.

Claims 1-4 and 7-8 (and 11, now canceled) remain rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent 4,895,724, issued to Cardinal et al. (hereinafter referred to as the Cardinal reference) in view of U.S. Patent 6,214,331, issued to Vanderhoff et al. (hereinafter referred to as the Vanderhoff reference). The examiner again asserted that Cardinal teaches a porous matrix of chitosan and a macromolecular compound, which can be a polysaccharide, such as dextran or heparin, dispersed therein. The compositions are for the controlled and prolonged release of the macromolecular compounds dispersed within the chitosan matrix, and higher amounts of cross-linking are said to lower the release rate of the macromolecular compound. The examiner noted that Cardinal does not disclose the  $\beta$ -(1,3) glucan feature of the compositions of the present claims, but he asserted that this deficiency is provided by Vanderhoff. The secondary reference was said to disclose a process for the preparation of aqueous dispersions of particle of water-soluble polymers, wherein cross-linking agents are used to cross-link the functional groups of the polymers. Useful polymers include polysaccharides such as curdlan, which is a  $\beta$ -(1,3) glucan. The examiner asserted that it would have been obvious to combine the

teachings of the two references to use curdlan in the invention of Cardinal to arrive at the present invention.

A key aspect of the present invention, as Applicants previously have argued, is that the chitosans and glucans are cross-linked to each other. Cardinal's preparations, in contrast, comprise cross-linked chitosans with a macromolecular compound dispersed therein. Applicants previously have pointed out that Cardinal's compositions do not comprise chitosans which are cross-linked to the macromolecules; rather, the chitosans are cross-linked to other chitosans. It is not appropriate for the macromolecules to be cross-linked to a chitosan matrix in Cardinal's slow release preparations since, if they were, they could not be released.

In the most recent Office Action, the examiner stated that "[t]herefore Cardinal's teachings of cross-linked chitosan matrix with macromolecules dispersed therein ..." (emphasis added), thereby acknowledging the difference between Cardinal's composition and that of the present invention. The examiner, however, also asserted that "[i]t appears [that the] applicants are arguing a specific formula for the resulting chitosans and glucans. However, the instant claims do not reflect this particular formula or the structure [which the] applicants argue is claimed." From these statements, it appears that the examiner interpreted claim 1 as previously presented as requiring only that the glucans are cross-linked and claim 2 as requiring an initial step of admixing the glucans and chitosans, then adding the cross-linking agent, then removing water but not that the glucans and chitosans are cross-linked to each other through the diisocyanates and dialdehydes. The statement on page 1, lines 31-34, of the specification, however, makes clear that the

preparations of the present invention comprise chitosans cross-linked to glucans via diisocyanates or dialdehydes, and claim 1 has been amended to make this more explicit.

Furthermore, the Examples of the present application provide additional evidence of the cross-linking between chitosans and glucans. In the Examples, the chitosans and glucans are admixed and then cross-linking agents are added. One of skill in the art would expect that this would result in the chitosans and glucans being cross-linked to each other (even if there also is some cross-linking of glucan to glucan and chitosan to chitosan), since both reactive species are present and no special conditions are disclosed which would prevent such cross-linking from occurring. In the Cardinal reference, if the macromolecule (glucan) and chitosans are both present prior to the addition of the cross-linking agent, the cross-linking agents used are large and "generally not capable of penetrating the chitosan matrix and affecting the macromolecule in the matrix" (column 5, lines 8-22). Thus, there is an explicit teaching by Cardinal that when cross-linking occurs after the incorporation of the macromolecule, the choice of cross-linking agents is such that the macromolecule is not affected, i.e., cross-linked.

The examiner has asserted that Cardinal discloses a method comprising the steps of present claim 2 (assuming that one substitutes dextran for curdlan on the basis of Vanderhoff). As noted above, Cardinal uses particular cross-linking agents to avoid cross-linking the macromolecule (curdlan/glucan) to the chitosan matrix. Claim 2 has been amended above to be dependent on claim 1; it thus is limited to the production of preparations with chitosans and glucans cross-linked to one another.

Applicants respectfully submit that the foregoing discussion and the amendments to claims 1 and 2 make clear that the composition of claim 1 and method of claim 2 are patentable over the Cardinal and Vanderhoff references. Accordingly, the dependent claims also included in this rejection also are patentable over the cited references.

The examiner has maintained her previous rejection of claims 5-6 under 35 U.S.C. § 103(a) as unpatentable over the Cardinal and Vanderhoff references cited above in further view of U.S. Patent 4,879,340, issued to Moriguchi et al. She also has maintained her previous rejection of claim 9 under this same section of the statute as unpatentable over the Cardinal and Vanderhoff references in further view of U.S. Patent 6,162,537, issued to Martin et al. She further has maintained her rejection of claim 10 under 35 U.S.C. § 103(a) as unpatentable over the Cardinal and Vanderhoff references in further view of U.S. Patent 6,096,344, issued to Liu et al. Each of these rejections is traversed.

The shortcomings of the Cardinal and Vanderhoff references have been discussed above, and that discussion is equally applicable to the rejections of dependent claims 5, 6, 9 and 10. The cited tertiary references do not compensate for the deficiencies of the primary and secondary references and are insufficient to render obvious the subject matter of these claims.

The examiner has issued a new rejection of claims 1-11 (now claims 1-10) as unpatentable over DE 9643066 (hereinafter referred to as DE '066) in view of Adachi et al., *Chem. Pharm. Bull.* 1990 (hereinafter referred to as Adachi). The examiner asserted that DE '066 is directed to a collagen free cosmetic

preparation formed by cross-linking cationic biopolymers, such as chitosan, with polyols and diisocyanates and/or dialdehydes, followed by water removal. The examiner acknowledged that the reference does not teach that the polyol is a  $\beta$ -(1,3)-glucan, but she asserted that this deficiency is cured by Adachi et al. This reference was characterized as teaching macrophage activation by chemically cross-linked  $\beta$ -(1,3)-glucans, which were said to have anti-tumor and gel-forming activity. Adachi et al. further stated that the cross-linking of glucans was important for the manifestation of biological activity. The examiner asserted that it would have been obvious to combine the teachings of the two references as one of skill in the art would have been motivated to use beta glucans as they are known polyols with anti-tumor activity and biological activity which is manifested by cross-linking. As DE '066 teaches the utilization of polyols for cross-linking to chitosan with additional cross-linking agents, such as dialdehydes and diisocyanates, one of ordinary skill in the art would have been motivated to use  $\beta$ -glucans to provide anti-tumor activity to the compositions taught by Adachi et al. This rejection is traversed.

DE '066 is discussed on page 1 of the present application and discloses a collagen free cosmetic preparation in which chitosans are cross-linked to one another. Contrary to the examiner's assertion, one of ordinary skill in the art looking to modify the teachings of DE '066 would not look to the teachings of Adachi et al. As noted on page 1 of the present application, preparations made in accordance with DE '066 have unsatisfactory dermatological compatibility. One of skill in the art looking to prepare a cosmetic preparation with improved dermatological compatibility would not look to Adachi et al., as that reference

is focused on the ability of different glucans, including various cross-linked glucans, to activate macrophages. The Adachi et al. reference clearly is not in the cosmetic field.

Furthermore, even if one of skill in the art were to look to Adachi et al., he would not consider it either reasonable or obvious to select a glucan of Adachi et al. as a "polyol" for use in the preparations of DE '066. Most scientists would not even consider a glucan to be a polyol. The polyols of the '066 application "preferably possess 2 to 15 carbon atoms (page 2). Examples listed in the '066 reference include "sugar alcohols with 5 to 12 carbon atoms," e.g., "sorbitol or mannitol" and "sugar with 5 to 12 carbon atoms," e.g., "glucose or sucrose."

In contrast, glucans are large macromolecules comprising at least many hundreds of linked glucose residues. Adachi et al. are concerned primarily with high molecular weight glucans (see page 98, left hand column, first sentence). Even the low MW glucans considered in the Adachi reference are 6400 to 21000 Da--clearly larger than the polyols considered suitable by the inventors of the '066 reference.

As further evidence in support of Applicants' position, Applicants note that the polyols are disclosed in the present application as optional additional components of the preparations; i.e., they are a different class of compound from the glucans. The combination of the teachings of DE '066 and the Adachi reference thus do not render obvious the presently claimed invention.

In view of the foregoing amendments and discussion,  
Applicants respectfully submit that the pending claims are in  
condition for allowance.

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